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Inverse Relationship of Blood Pressure Levels to Sudden Cardiac Mortality and Benefit of the Implantable Cardioverter-Defibrillator in Patients With Ischemic Left Ventricular Dysfunction

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Objectives This study was designed to evaluate the relationship among blood pressure (BP) levels, risk of sudden cardiac death (SCD), and benefit of the implantable cardioverter-defibrillator (ICD) in patients with ischemic left ventricular (LV) dysfunction.

Background Low BP has been shown to be associated with increased mortality in patients with LV dysfunction and heart failure. We hypothesized that increasing BP levels are associated with a reduction in the risk of SCD in this population, thereby limiting ICD efficacy in a lower-risk subset.

Methods The independent contribution of systolic blood pressure (SBP) and diastolic blood pressure (DBP) to outcome was analyzed in 1,231 patients enrolled in the prospective MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II).

Results Multivariate analysis showed that in the conventional therapy arm of the trial, 10-mm Hg increments in systolic BP were independently associated with a respective 14% ($p = 0.01$) and 16% ($p = 0.04$) reduction in the risk of cardiac mortality and SCD; similar trends were shown for DBP. Defibrillator therapy provided the least survival benefit to patients in the lower-risk, upper SBP (>130 mm Hg) and DBP (≥80 mm Hg) quartiles (hazard ratio 1.04 [$p = 0.89$] and 1.05 [$p = 0.88$], respectively), whereas a respective 39% and 38% ($p = 0.002$) reduction in the risk of death with ICD therapy was observed among patients with lower BP values.

Conclusions In patients with ischemic LV dysfunction, SBP and DBP levels show an inverse correlation with sudden cardiac mortality. These noninvasive hemodynamic parameters may be useful for identifying lower-risk patients, in whom the benefit of primary defibrillator implantation is more limited. (J Am Coll Cardiol 2007;49:1427–33)

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Patients with a low ejection fraction (EF) and heart failure have been shown to be at a high risk for arrhythmic mortality and to obtain a survival benefit with the implantable cardioverter-defibrillator (ICD) (1–4). However, only about one-third of the patients in whom an ICD is implanted for the primary prevention of sudden cardiac death (SCD) require device therapy for ventricular tachyarrhythmias during long-term follow-up (5). Thus, the benefit of the ICD may be more limited in a lower-risk subset of low EF patients.

Previous studies that have evaluated patients with left ventricular (LV) dysfunction and heart failure have shown an inverse correlation between blood pressure (BP) levels and the risk of all-cause mortality (6–13). However, the relationship between BP levels and the risk of arrhythmic mortality in this population has not been assessed. We hypothesized that in patients with ischemic LV dysfunction enrolled in the prospective MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) study, BP levels would show a similar inverse correlation with SCD risk, and that this relationship may provide a useful risk stratification parameter for primary ICD implantation.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
DBP = diastolic blood pressure
EF = ejection fraction
ICD = implantable cardioverter-defibrillator
LV = left ventricular
MADIT-II = Multicenter Automatic Defibrillator Implantation Trial II
MI = myocardial infarction
NYHA = New York Heart Association
SBP = systolic blood pressure
SCD = sudden cardiac death

Methods

MADIT-II. The design and results of MADIT-II have been reported elsewhere (4). Briefly, 1,232 patients with documented previous myocardial infarction (MI), EF ≤30%, and New York Heart Association (NYHA) functional class I to III were randomized to receive a prophylactic ICD or conventional medical therapy in a 3:2 ratio and were followed up over a mean period of 20 months. Screened patients were excluded from enrollment if they had class IV congestive heart failure, coronary revascularization within the previous 3 months, elapsed interval from most recent MI of <1 month, or advanced medical comorbidity. Baseline BP values were recorded during enrollment, and were not available for 1 patient. The remaining 1,231 patients were included in the present study, of whom 742 patients were allocated to the ICD arm and 489 patients were allocated to the conventional therapy arm of the trial.

Definitions and outcome. The BP indexes evaluated in the current study included systolic blood pressure (SBP) and diastolic blood pressure (DBP). Blood pressure values were analyzed by: 1) dividing BP indexes into approximate quartiles (SBP: <100, 100 to 119, 120 to 130, and ≥130 mm Hg; DBP: ≤60, 61 to 69, 70 to 79, and ≥80 mm Hg; with somewhat unequal numbers per quartile because of a high concentration of subjects at the decile values) and 2) including BP indexes as continuous measures in the multivariate models. The effect of BP on the end points of all-cause mortality, cardiac death, and SCD was examined in the conventional therapy arm, and the efficacy of ICD therapy in reducing the risk of death was analyzed within the prespecified BP quartiles. A modified Hinkle-Thaler system was used to classify deaths as previously described (14).

Statistical analysis. Baseline characteristics by BP quartiles were compared and contrasted using the chi-square test. Kaplan-Meier estimates, stratified by BP quartiles, for all-cause mortality in each treatment group were determined and statistically evaluated with the log-rank test. The Cox proportional hazards regression model was used to evaluate

Table 1 Baseline Characteristics of Study Patients by SBP Quartiles

Characteristic	SBP (mm Hg) <100 (n = 288)	100–119 (n = 256)	120–130 (n = 344)	>130 (n = 343)	p Value*
SBP (mm Hg, mean ± SD)	99 ± 7	113 ± 3	124 ± 4	145 ± 12	NA
DBP (mm Hg, mean ± SD)	62 ± 8	69 ± 8	73 ± 9	78 ± 11	NA
Age >65 yrs (%)	48	48	54	62	<0.001
Female gender (%)	14	16	16	16	0.82
NYHA functional class ≥2 (%)†	69	59	64	63	0.11
Angina pectoris functional class ≥2 (%)†	30	28	30	26	0.61
BUN >25 mg/dl (%)	38	31	27	27	0.01
History of hypertension (%)	42	45	54	69	<0.001
Diabetes mellitus (%)	30	34	38	37	0.09
Past CABG (%)	57	55	58	59	0.76
LBBB (%)	21	21	15	17	
QRS duration >0.12 (%)	42	38	33	35	0.16
EF <25%	62	50	45	39	<0.001
Atrial fibrillation (%)	9	9	7	9	0.76
Cigarette smoking anytime (%)	79	82	83	78	0.41
Heart rate ≥80 beats/min per ECG (%)	34	27	26	28	0.21
BMI ≥30 kg/m^2 (%)	26	30	28	32	0.39
Medical therapy					
ACE inhibitors (%)	77	74	78	79	0.56
ARBs (%)	11	14	12	13	0.57
Digitalis (%)	65	60	54	56	0.03
Beta-blockers (%)	62	63	62	62	0.99
Amiodarone (%)	6	5	7	10	0.08
Lipid-lowering agents (%)‡	66	63	67	67	0.66
Diuretics (%)	79	76	72	73	0.17

*p value for comparison of the distribution among the 4 SBP quartiles. †New York Heart Association (NYHA) and angina functional class represent the highest class during the 3 months before enrollment. ‡Statins comprised 95% of lipid-lowering agents.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BUN = blood urea nitrogen; CABG = coronary artery bypass graft surgery; DBP = diastolic blood pressure; ECG = electrocardiogram; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; PP = pulse pressure; SBP = systolic blood pressure.

the independent contribution of baseline clinical factors to the development of end points. The baseline variables that had differences among the 4 SBP and DBP quartile groups, using a p value <0.10, were evaluated in the proportional hazards stepwise selection model. Covariates with a p value <0.05 in the proportional hazards model were included in the final model. In an alternative analysis, gender, NYHA functional class, QRS duration >0.12 s, heart rate ≥80 beats/min, and medical therapy with beta-blockers and angiotensin-converting enzyme (ACE) inhibitors were forced into the multivariate models as additional covariates. The effect of BP on the end points of all-cause mortality, cardiac death, and SCD in the conventional therapy arm, and ICD efficacy by BP subgroups was examined in a total population model by including a treatment × BP interaction term. All p values were 2-sided, and a value of $p < 0.05$ was considered significant. Analyses were performed using SAS software (version 9.13, SAS Institute Inc., Cary, North Carolina).

Results

Baseline BP indexes were normally distributed among study patients and were similar in the ICD and conventional therapy groups. The mean (± SD) SBP and DBP among study patients was 122 ± 18 mm Hg and 71 ± 11 mm Hg, respectively.

Baseline laboratory and clinical characteristics of study patients by SBP quartile categories are shown in Table 1. The mean DBP correlated with SBP quartiles. The proportion of patients with an older age, a history of hypertension, and diabetes mellitus increased with increasing SBP quartiles, whereas the proportion of patients with a lower EF and higher baseline blood urea creatinine levels was inversely correlated with SBP. Medical therapies with ACE inhibitors, beta-blockers, and lipid-lowering agents were administered to a similar proportion of patients among SBP quartiles, whereas therapy with digitalis was administered to a higher proportion of patients with low SBP. Baseline clinical characteristics and medical therapies were similarly distributed among DBP quartiles (not shown).

Blood pressure indexes and mortality in the conventional therapy group. Baseline variables that showed differences among the 4 SBP and DBP quartiles and were significantly associated with each outcome measure included age >65 years, EF <25%, and blood urea nitrogen >25 mg/dl (Table 2). The effect of SBP and DBP on outcome in the conventional therapy group, after adjustment for these baselines covariates, is presented in Table 2.

The risk of cardiac and SCD declined by 14% and 16%, respectively, for every 10-mm Hg increment in SBP, and by 18% and 20%, respectively, for every 10-mm Hg increment in DBP. Quartile analysis showed a significant reduction in the risk of all-cause mortality and cardiac death with increasing BP quartiles, whereas the decline in the risk of SCD was apparent mainly among patients with upper-quartile SBP (59% reduction) and DBP (67% reduction)

Table 2 Multivariate Analysis: Predictors of Outcome in the Baseline Model and Effect of Blood Pressure Levels on Outcome in the Conventional Therapy Group

	All-Cause Mortality		Cardiac Death		SCD	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Baseline model*						
ICD vs. conventional	0.68 (0.51–0.89)	0.005	0.62 (0.46–0.85)	0.003	0.36 (0.22–0.57)	<0.001
Age >65 yrs	1.82 (1.34–2.49)	<0.001	1.64 (1.17–2.32)	0.005	2.08 (1.24–3.47)	0.005
EF <25%	1.55 (1.17–2.06)	0.003	1.58 (1.15–2.17)	0.005	1.98 (1.24–3.17)	0.004
BUN >25 mg/dl	2.21 (1.66–2.96)	<0.001	2.49 (1.80–3.45)	<0.001	1.99 (1.25–3.18)	0.004
SBP (mm Hg)†						
Continuous analysis						
Per 10-mm Hg increase	0.85 (0.76–0.95)	0.005	0.86 (0.76–0.97)	0.01	0.84 (0.71–0.99)	0.04
Quartile analysis						
Q_2 (100–119) vs. Q_1 (<100)	0.88 (0.51–1.52)	0.65	0.88 (0.48–1.62)	0.69	1.02 (0.46–2.25)	0.96
Q_3 (110–119) vs. Q_1 (<100)	0.74 (0.44–1.25)	0.26	0.76 (0.43–1.34)	0.34	0.99 (0.48–2.04)	0.98
Q_4 (120–130) vs. Q_1 (<100)	0.41 (0.22–0.77)	0.005	0.47 (0.24–0.92)	0.02	0.41 (0.17–0.97)	0.04
DBP (mm Hg)†						
Continuous analysis						
Per 10-mm Hg increase	0.79 (0.64–0.97)	0.02	0.82 (0.65–1.02)	0.07	0.80 (0.60–1.05)	0.09
Quartile analysis						
Q_2 (61–69) vs. Q_1 (≤60)	0.71 (0.40–1.25)	0.23	0.76 (0.41–1.43)	0.40	0.51 (0.22–1.17)	0.11
Q_3 (70–79) vs. Q_1 (≤60)	0.60 (0.37–0.98)	0.04	0.68 (0.40–1.17)	0.17	0.58 (0.30–1.12)	0.10
Q_4 (≥80) vs. Q_1 (≤60)	0.41 (0.21–0.78)	0.007	0.40 (0.19–0.84)	0.01	0.33 (0.13–0.84)	0.02

*The baseline model includes variables that had differences between the 4 SBP and DBP quartile groups, using a p value <0.10, which were evaluated in the proportional hazards stepwise selection model and had a p value <0.05. †Models were analyzed in the total population and adjusted for age >65 yrs, BUN ≥25 mg/dl, EF <25%, treatment group, BP category, and treatment group × BP interaction; the main effects of age, BUN, and EF in the SBP and DBP models were virtually identical to those presented for the baseline model; findings were similar after further adjustment for gender, NYHA functional class, QRS duration >0.12 s, heart rate ≥80 beats/min, and medical therapy with beta-blockers and angiotensin-converting enzyme inhibitors; no significant treatment × BP interaction was shown for all end points.

CI = confidence interval; HR = hazard ratio; SCD = sudden cardiac death; other abbreviations as in Table 1.

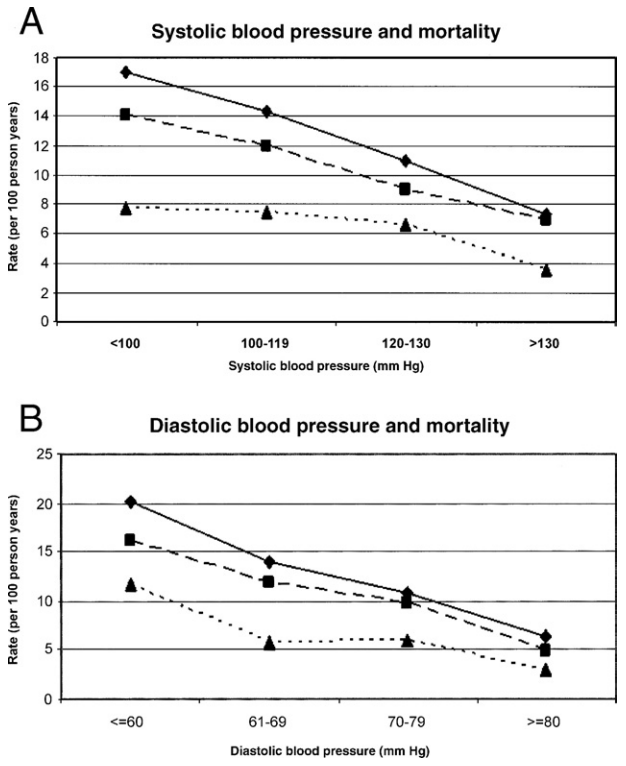

Figure 1 **Mortality Rates by Systolic and Diastolic Blood Pressure**

All-cause **(solid diamonds, solid lines)**, cardiac **(solid squares, dashed lines)** and sudden cardiac **(solid circles, dotted lines)** mortality rates per 100 person-years by **(A)** systolic blood pressure quartiles and **(B)** diastolic blood pressure quartiles.

values (Table 2). Consistently, the relationship between SBP and DBP and mortality (Figs. 1A and 1B) showed a linear reduction in the rates of all-cause and cardiac mortality with increasing SBP (>2-fold decrease) and DBP quartiles (>3-fold decrease), whereas the decline in the rate of SCD with increasing SBP and DBP quartiles was nonlinear, and was prominent mainly among patients in the upper BP quartiles.

Relationship of BP indexes to ICD benefit. In multivariate analysis, defibrillator therapy was associated with an overall significant 32% reduction in the risk of death in the total study population (Table 2). When ICD efficacy was analyzed within BP subgroups (Table 3), no survival benefit was shown among patients with SBP >130 mm Hg and DBP ≥80 mm Hg (hazard ratio [HR] 1.04 [p = 0.89] and 1.05 [p = 0.88], respectively), whereas among patients with SBP ≤130 mm Hg and DBP <80 mm Hg, defibrillator therapy was associated with a respective 39% (p = 0.002) and 38% (p = 0.002) reduction in mortality risk. The benefit of the ICD was consistent within the individual lower 3 SBP and DBP quartiles (Table 3), whereas no ICD benefit was consistently shown when narrower ranges within the SBP >130 mm Hg quartile (131 to 140 mm Hg: HR 1.05 [p = 0.87]; >140 mm Hg: HR 1.02 [p = 0.69]) and the DBP ≥80 mm Hg quartile (80 to 85 mm Hg: HR 1.18 [p = 0.64]; >85 mm Hg: HR 0.97 [p = 0.94]) were analyzed. Accordingly, Kaplan-Meier survival curves in the 2 treatment groups among patients with SBP <130 mm Hg and DBP ≤80 mm Hg (Figs. 2A and 3A, respectively) showed a significantly lower 2-year mortality rate in the ICD group (17%) compared with the conventional therapy group (25%), whereas the 2-year probability of death was similar in the ICD and conventional therapy groups among patients with SBP >130 mm Hg (13% and 12%, respectively) (Fig. 2B) and DBP ≥80 mm Hg (11% and 12%, respectively) (Fig. 3B).

In a further exploratory analysis, ICD efficacy among patients in whom both SBP and DBP levels were elevated at the upper quartile (n = 172) was compared with the benefit of device therapy among all other study patients (in whom either SBP or DBP levels [or both] were below the respective upper quartile value [n = 1,059]). In the former subgroup of lower-risk patients, no ICD benefit was observed (HR 2.43 [95% confidence interval 0.70 to 8.48]; p = 0.16), whereas in the latter subgroup defibrillator therapy was associated with a significant survival benefit (HR 0.62 [95% confidence interval 0.46 to 0.82]; p = 0.001). Notably, a significant ICD × BP interaction was shown for the comparison of ICD benefit between the 2 subgroups (p = 0.03), suggesting a significant reduction in ICD efficacy among patients who maintained elevated levels of both SBP and DBP.

Discussion

The main finding of this study is that patients with ischemic LV dysfunction who maintain elevated SBP and DBP have

Table 3 **Survival Benefit of ICD by SBP and DBP Quartiles***

	HR	95% CI	p Value
SBP (mm Hg)			
Q_4: >130† (n = 343)	1.04	0.55–1.97	0.89
Q_{1-3}: ≤130† (n = 888)	0.61	0.45–0.83	0.002
Q_1: <100 (n = 288)	0.65	0.40–1.07	0.09
Q_2: 100–119 (n = 256)	0.56	0.31–1.00	0.05
Q_3: 120–130 (n = 344)	0.62	0.36–1.06	0.08
DBP (mm Hg)			
Q_4: ≥80‡ (n = 328)	1.05	0.54–2.05	0.88
Q_{1-3}: <80‡ (n = 903)	0.62	0.46–0.84	0.002
Q_1: ≤60 (n = 286)	0.57	0.35–0.93	0.02
Q_2: 61–69 (n = 210)	0.60	0.31–1.11	0.10
Q_3: 70–79 (n = 407)	0.65	0.40–1.07	0.09

*HR indicates the ICD versus conventional risk of death within each blood pressure quartile; findings were adjusted for age >65 yrs, BUN ≥25 mg/dl, EF <25%, treatment group, BP category, and treatment group × BP category interaction; the main effects of age, BUN, and EF in each BP model were nearly identical to those presented in Table 2; findings were similar after further adjustment for gender, NYHA functional class, QRS duration >0.12 s, heart rate ≥80 beats/min, and medical therapy with beta-blockers and ACE inhibitors; no significant interaction between medical therapy with either beta-blockers or ACE inhibitors and ICD benefit was observed within analyzed BP categories. †p value for treatment × SBP category interaction = 0.13. ‡p value for treatment × DBP category interaction = 0.11.

Abbreviations as in Tables 1 and 2.

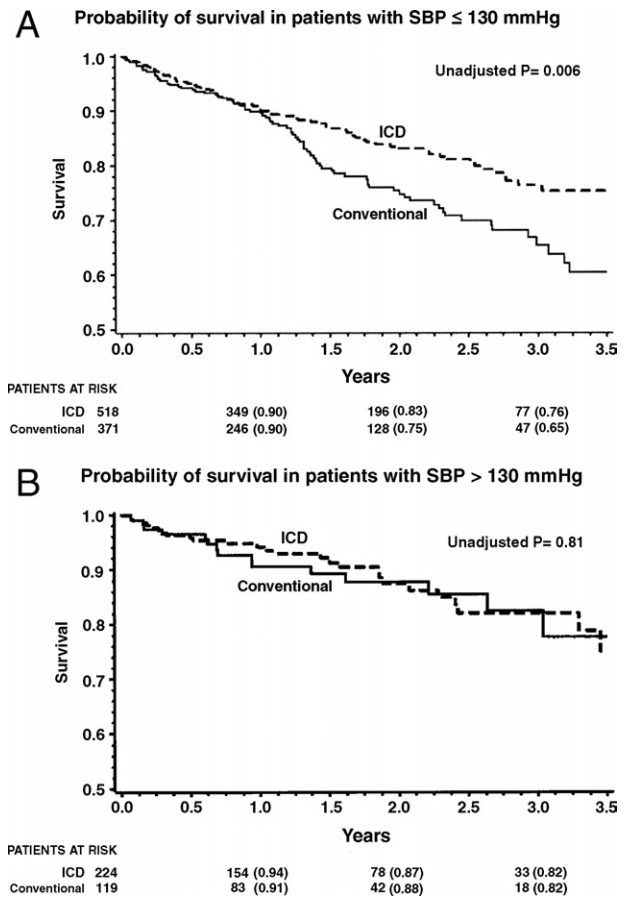

Figure 2 ICD Benefit by SBP

Kaplan-Meier estimates of probability of all-cause mortality by treatment group among patients with **(A)** systolic blood pressure (SBP) quartiles 1 to 3 and **(B)** SBP quartile 4. ICD = implantable cardioverter-defibrillator.

a lower risk of SCD, and that these noninvasive hemodynamic indexes may be useful for identifying higher-risk and lower-risk subgroups within the low EF population when primary ICD implantation is considered.

Abundant data from major trials have consistently shown the detrimental cardiovascular effects of hypertension and the established benefit of treating hypertension in reducing the risk of heart failure and cardiovascular mortality (15–17). These studies, however, have focused on younger hypertensive patients, mostly with preserved cardiac function. Our finding that high, not low, BP is predictive of favorable survival in patients with reduced LV function (≤30%) and a compensated heart failure functional class is consistent with previous published data in this population (6–13). However, in the current study we extended these observations, and have shown that increased systolic and diastolic pressures are also associated with a reduction in the risk of sudden cardiac mortality.

Low EF had been identified as a risk factor for subsequent cardiac mortality and SCD (18), and has become the major criterion for primary prevention with ICD therapy (19). However, data from MADIT-II have shown that only approximately one-third of patients received appropriate ICD therapy for ventricular tachycardia or fibrillation throughout the course of the trial (5). Therefore, it is important to identify low-risk patients within the low EF group. To date, suggested risk factors, including QRS duration or advanced NYHA functional class, were not shown to stratify patients with LV dysfunction into high-risk and low-risk groups (4). Furthermore, inducibility with electrophysiological testing was not shown to be clinically useful in identifying patients who should receive primary ICD implantation for the prevention of SCD (20). In the current study we have shown that noninvasive BP indexes identify patients with a lower risk of SCD, and therefore may be useful in risk stratification for primary ICD therapy in patients with advanced LV dysfunction. The decline in the rate of SCD with increasing BP values was nonlinear, and was prominent mainly among patients in the upper SBP and DBP quartiles. Accordingly, these lower-risk subgroups

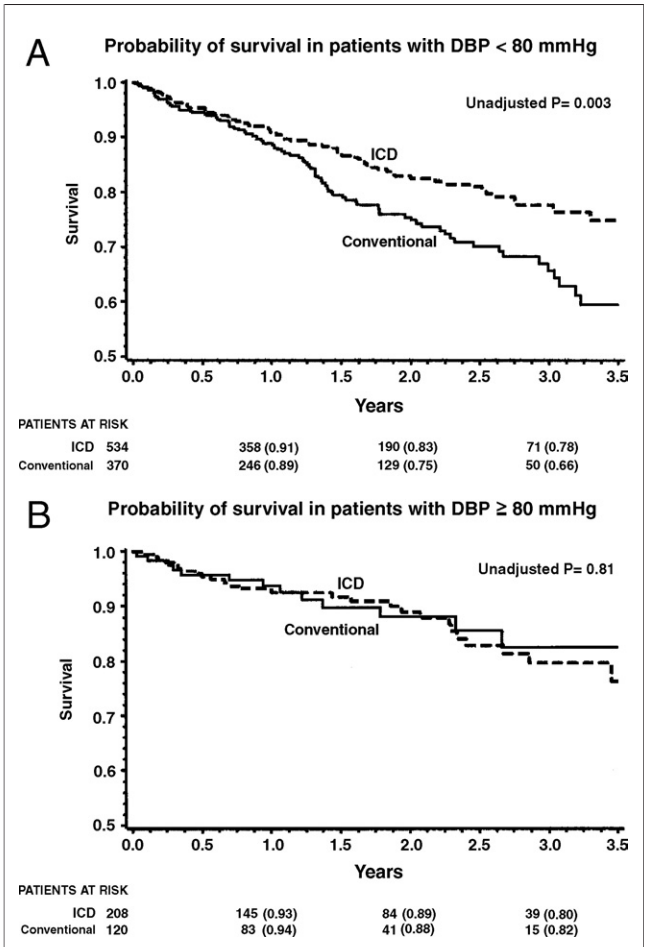

Figure 3 ICD Benefit by DBP

Kaplan-Meier estimates of probability of all-cause mortality by treatment group among patients with **(A)** diastolic blood pressure (DBP) quartiles 1 to 3 and **(B)** DBP quartile 4. ICD = implantable cardioverter-defibrillator.

received the least benefit from primary ICD implantation. Moreover, a significant interaction effect was shown between ICD therapy and the BP category comprising patients who maintained elevated levels of both SBP and DBP, suggesting that the benefit of the ICD is significantly attenuated in this subset of patients.

Notably, the relationship between ICD efficacy and BP persisted after multivariate adjustment for EF, NYHA functional class, heart rate, or concurrent therapies with BP-lowering medications. Therefore, our findings regarding the effect of BP on outcome seem to be independent of other markers of health in this population. The ability to maintain elevated systolic and diastolic pressures despite a low EF may indicate better myocardial reserve, which possibly may be associated with improved survival and reduced risk of cardiac and SCD. It is also possible that in patients with LV dysfunction who have lower BP levels, there is maladaptive activation of catecholamine and other neurohormonal counter-regulatory systems that potentially contribute to increased risk for arrhythmias and death.

Study limitations. Several limitations of this study should be noted. No conclusions on the benefit of antihypertensive treatment or current medical therapy recommendation for patients with heart failure can be drawn on the basis of this study. Beta-blockers and ACE inhibitors have been shown to prolong life in this high-risk population, and should be administered to every patient with advanced LV dysfunction without contraindications.

The power of this subanalysis of MADIT-II to detect a statistically significant ICD survival benefit within individual BP quartiles was limited because of a relatively small sample size. However, within each of the lower 3 SBP and DBP quartiles we observed similar trends for ICD efficacy, whereas among the upper SBP and DBP quartiles no ICD benefit was shown after multivariate adjustment. Furthermore, despite a relatively small sample size, we observed a marginally significant treatment × BP interaction when the upper SBP and DBP quartiles were compared with the respective lower 3 BP quartiles, and a statistically significant reduction in ICD efficacy among patients who maintained elevated levels of both SBP and DBP.

Beta-blockers were administered to approximately two-thirds of study patients. Therefore, the current results may not represent the effect of BP on outcome in patients who are receiving full medical therapy for heart failure. However, our findings regarding ICD efficacy within the BP subgroups persisted after multivariate adjustment for medical therapies, and no interaction was shown between the effects of beta-blockers or ACE inhibitors on outcome and ICD efficacy, suggesting that the findings regarding the relationship among BP, risk of SCD, and ICD benefit are independent of adjunctive medical therapies.

The present study results are only applicable to the MADIT-II study population, which is composed of patients with coronary heart disease and LV dysfunction. Therefore, data on the relationship between BP and ICD benefit in patients with nonischemic cardiomyopathy cannot be derived from the current analysis. In addition, follow-up data on BP levels were not consistently collected in MADIT-II, precluding a comprehensive analysis of the effect of time-dependent changes in BP on outcome.

Conclusions

We have shown that patients with ischemic LV dysfunction who maintain elevated SBP and DBP have a lower risk of SCD, and may therefore derive less benefit from primary ICD implantation. Validation of these findings in subanalyses of major randomized ICD trials and the ongoing MADIT-II ICD Registry would provide important prognostic data in this high-risk population. At present, our findings suggest that follow-up of BP levels should be an important component of risk assessment in patients considered for primary ICD implantation.

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